REVIEW ARTICLE

# Recommendations for (Discontinuation of) Statin Treatment in Older Adults: Review of Guidelines

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**OBJECTIVES:** As a person's age increases and his/her health status declines, new challenges arise that may lead physicians to consider deprescribing statins. We aimed to provide insight into recommendations available in international cardiovascular disease prevention guidelines regarding discontinuation of statin treatment applicable to older adults.

**DESIGN:** We systematically searched PubMed, EMBASE, EMCARE, and the websites of guideline development organizations and online guideline repositories for cardiovascular disease prevention guidelines aimed at the general population. We selected all guidelines with recommendations (instructions and suggestions) on discontinuation of statin treatment applicable to older adults, published between January 2009 and April 2019. In addition, we performed a synthesis of information from all other recommendations for older adults regarding statin treatment. Methodological quality of the included guidelines was appraised using the appraisal of guidelines for research & evaluation II (AGREE II) instrument.

**RESULTS:** Eighteen international guidelines for cardiovascular disease prevention in the general adult population provided recommendations for statin discontinuation that were applicable to older adults. We identified three groups of instructions for statin discontinuation related to statin intolerance, and none was specifically aimed at older adults. Three guidelines also included suggestions to consider statin discontinuation in patients with poor health status. Of the 18 guidelines included, 16 made recommendations regarding statin treatment in older adults, although details on how to implement these recommendations in practice were not provided.

**CONCLUSION:** Current international cardiovascular disease prevention guidelines provide little specific guidance for physicians who are considering statin discontinuation in older adults in the context of declining health status and short life expectancy. **J Am Geriatr Soc 00:1-9, 2019.**

**Key words: cardiovascular diseases; clinical decision making; drug therapy; hydroxymethylglutaryl-CoA reductase inhibitors; prevention**

Up to the age of approximately 75 years, the effectiveness of cardiovascular preventive medication is undisputed and, together with lifestyle interventions, significantly reduces the impact of cardiovascular disease.[1-3] Also, for vital adults aged 75 to 85 years, there is evidence that the benefits of statins generally outweigh the risks, especially in secondary prevention.[4,5] However, when confronted with declining health status and the development of complex health problems, the use of preventive medications with long-term effects might become of questionable benefit; on the one hand, treatment priorities shift and life expectancy shortens, while on the other hand, the risks of adverse effects increase due to pharmacokinetic and pharmacodynamic changes, polypharmacy, and multimorbidity,[6-9] especially in old age. These risks can be influenced positively by decreasing medication prescriptions. In addition, high-quality evidence is not yet available for either primary or secondary statin-based prevention in people aged 85 years and older or in those with complex health problems (as they are currently excluded from trials).[10] In a recent meta-analysis of the efficacy and safety of statins for primary cardiovascular disease prevention in older adults, which included data

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from 28 trials, only 8% of all patients were aged older than 75 years at enrollment.[5] As statins are one of the most commonly used drugs in the older population, with a prevalence ranging between 18% and 45%,[11,12] with concerns about the benefits, they have been identified as possible candidates for deprescribing (the process of tapering or stopping inappropriate medication) by both clinicians and patients.[10,11,13-19] In a modified Delphi approach, physicians, pharmacists, and nurses prioritized statins in the top three of a list of medication classes where evidence-based deprescribing guidelines would be of benefit to clinicians because of concerns about benefit given the lack of older patients in trials, the lack of clarity around ongoing indication and when they can be stopped, as well as an emerging recognition of adverse effects and overtreatment of low-risk patients.[14]

Qualitative studies have shown that both physicians and patients are generally open to statin deprescription in the case of older adults.[19-22] Nevertheless, medications, including statins, are often continued until death.[17,23] It has been reported that physicians do not feel confident about deprescribing cardiovascular preventive medication and survey studies have found considerable treatment variation in the advice regarding discontinuation of preventive medication.[22,24,25] A likely contributing factor and an acknowledged barrier to deprescribing medications is the lack of

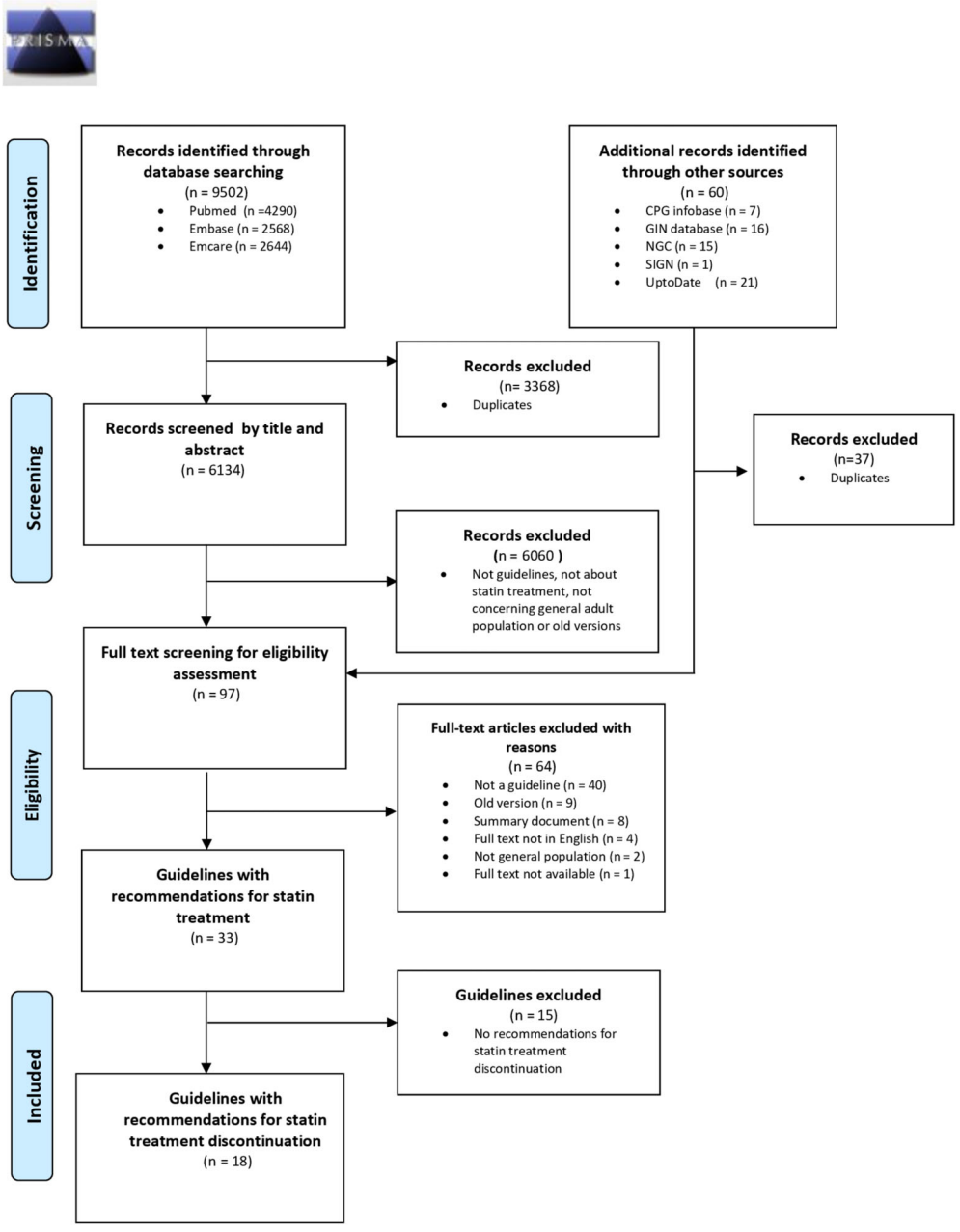


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing the selection process of the guidelines.CPG: Canadian Clinical Practice Guidelines InfoBase; G-I-N: Guidelines International Network; NGC: National Guideline Clearinghouse; SIGN Scottish Intercollegiate Guidelines Network (SIGN)

evidence and clear guidance in clinical practice guidelines.[10,21,25] Therefore, the primary objective of this systematic review was to provide insight into the available recommendations regarding statin treatment discontinuation in older adults as provided by international guidelines on cardiovascular disease prevention in the general population. To explore the context of recommendations for discontinuation applicable to older adults, we additionally analyzed which other recommendations were formulated concerning statin treatment in older adults.

## METHODS

### Search Strategy

#### *Identification and Screening of the Records*

Following consultation with an experienced health research librarian, we conducted systematic electronic searches in PubMed, Emcare, and Embase for references published from January 1, 2009 (search date April 23, 2019). We combined

**Table 1. Characteristics of Guidelines That Include Recommendations for Statin Discontinuation Applicable to Older Adults (n = 18)**

| Author | Year | Country | Organization | Age, y | Excluding | Intended users |
|---|---|---|---|---|---|---|
| Allan et al[28] | 2015 | Canada | TOP | NS | | Primary care clinicians and their teams |
| Catapano et al[29] | 2016 | Europe | ESC, EAS | All ages | | Healthcare professionals |
| Downs et al[30] | 2015 | United States | Va/DoD | Adults | Patients with severe systolic chronic heart failure, with end-stage renal disease, and on dialysis, or those with a limited life expectancy | Primary care providers |
| Fan et al[31] | 2014 | United States | UMHS | 20-79 | Patients with familial or severe dyslipidemias or chronic kidney disease | NS |
| Grundy et al[32] | 2018 | United States | ACC, AHA | ≥21 | | Primary care clinicians, specialists concerned with ASCVD prevention |
| Guerrero[33] | 2016 | Philippines | PHA, PLAS, PSEM | NS | | Filipino physicians |
| Jacobson et al[34] | 2015 | United States | NLA | All ages | | Clinicians |
| Jellinger et al[35] | 2017 | United States | AACE, ACE | All ages | | Endocrinologists |
| Kinoshita et al[36] | 2018 | Japan | JAS | All ages | | NS |
| Last et al[37] | 2011 | United States | | NS | | Family physicians |
| Lewis[38] | 2009 | United States | | NS | | Physicians |
| Li et al[39] | 2017 | Taiwan | TSLA | NS | | Healthcare professionals |
| MoH Malaysia[40] | 2017 | Malaysia | MoH Malaysia, NHAM, AM | All ages | | General practitioners, medical officers, pharmacists, general and family physician, cardiologists, and endocrinologists |
| MoH Qatar[41] | 2016 | Qatar | MoH Qatar | NS | | Physicians in both primary/ generalist and secondary/specialist care settings |
| NICE[42] | 2014 | United Kingdom | NICE | NS | (i.a.) People on renal replacement therapy | Healthcare professionals |
| NVDPA[43] | 2012 | Australia | NVDPA | Adults | | General practitioners, aboriginal health workers, other primary care health professionals and physicians |
| SIGN[44] | 2017 | United Kingdom | SIGN | All ages | People with chronic heart failure, acute coronary syndrome, stable angina, or cardiac arrhythmia | Healthcare professionals, public health staff, patients, caregivers, voluntary organizations, policy makers |
| Tai et al[45] | 2017 | Singapore | MoH Singapore | All ages | | All physicians, particularly primary care physicians |

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; AHA, America Heart Association; AM, the Academy of Medicine; ASCVD, atherosclerotic cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; i.a, if applicable; JAS, Japanese Atherosclerosis Society; MoH, Ministry of Health; NHAM, National Heart Association of Malaysia; NICE, National Institute for Health and Care Excellence; NLA, National Lipid Association; NS, not specified; NVDPA, National Vascular Disease Prevention Alliance; PHA, Philippine Heart Association; PLAS, Philippine Lipid and Atherosclerosis Society; PSEM, Philippine Society of Endocrinology, Diabetes, and Metabolism; SIGN, Scottish Intercollegiate Guidelines Network; TOP, Towards Optimized Practice; TSLA, Taiwan Society of Lipids and Atherosclerosis; UMHS, University of Michigan Health System; Va/DoD, Department of Veterans Affairs and the Department of Defense.

thesaurus terms and free text to define "statins," "cardiovascular diseases," "cholesterol," and "lipids" and terms for the concept "guideline" (Supplementary Text S1 provides the complete strategies). We additionally searched the following websites of guideline development organizations and guideline repositories: Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/); Guidelines International Network (G-I-N) (http://www.g-i-n.net/); National Guideline Clearinghouse (NGC) (https://www.guideline.gov/); Canadian Clinical Practice Guidelines Infobase (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx); and UpToDate (https://www.uptodate.com/contents/search). For the search, we used the same terminology on April 24, 2019, with the exception of the G-I-N database (access date April 12, 2018) due to inaccessibility of the G-I-N database from July 2018.

### *Study Selection*

After removal of duplicate records, one reviewer (M.P.) assessed the initial eligibility of the retrieved studies based on the title and abstract by checking the following exclusion criteria: (*a*) publication is not a guideline; (*b*) publication is not about statin treatment; (*c*) publication does not regard a general adult population (eg, disease- or population-specific guidelines, such as "patients with diabetes" or "patients with stroke"); guidelines for the general adult population that also include recommendations for secondary prevention were not excluded; (*d*) publication is an old version of a more recently published guideline; and (*e*) full text is not available in English. When there was any doubt based on the title, abstract, or publication information to determine the relevance, the publication was included for further assessment. Subsequently, two investigators (M.P. and Y.D.) assessed the full-text publications regarding inclusion and the already above mentioned exclusion criteria. The inclusion criteria were: (*a*) cardiovascular disease prevention guidelines concerning the general population and (*b*) published in the last 10 years. Additionally, the two investigators (M.P. and Y.D.) assessed the availability of recommendations for statin treatment discontinuation for older adults (third inclusion criterion). Guidelines without recommendations for statin discontinuation recommendations or with only recommendations not applicable to older adults (eg, pregnancy and lactation related) were excluded. During consensus meetings, the investigators compared their assessments and discussed differences until consensus was reached.

### Quality Assessment

Two investigators (M.P. and C.F.) assessed the methodological rigor of each guideline using the AGREE II instrument.[26] AGREE II consists of 23 items rated on a 7-point Likert scale (1 = strongly disagree [item is absent or poorly written] to 7 = strongly agree [the quality of the item is exceptional and full criteria articulated in the User Manual have been met]). AGREE II items are organized into six quality domains: (*a*) scope and purpose, (*b*) stakeholder involvement, (*c*) rigor of development, (*d*) clarity of presentation, (*e*) applicability, and (*f*) editorial independence, with a 24th item related to overall quality (Supplementary Text S2 provides more details about the rating process and the calculation of the scaled domain scores). The intraclass correlation coefficient (ICC) for interrater agreement on the total number of all ratings was calculated using SPSS, version 23.0 (SPSS Inc).

### Information Synthesis: Recommendations for Discontinuation and Other Recommendations for Older Adults

All recommendations for statin discontinuation applicable to older adults were summarized into groups with similar content. We have made a distinction between recommendations that were phrased in a directive way (instructions) and recommendations

**Table 2. Recommendations for Statin Discontinuation Applicable to Older Adults in 18 International Guidelines**

| Group | | No. of guidelines with this recommendation | Guidelines |
|---|---|---|---|
| Intolerance | **Should be discontinued (at least temporarily)**: | | |
| | • Muscle symptoms (including rhabdomyolysis) | 12 | 28,29,31-33,35,36,39,40,42,43,45 |
| | • Liver toxicity | 5 | 29,30,38,40,45 |
| | • Contraindication | 2 | 37,44 |
| | **Consider discontinuation/might not be appropriate (to continue)** | | |
| | • Muscle symptoms (including rhabdomyolysis) | 3 | 28,41,44 |
| | • Cognitive dysfunction after the start of statins (to assess reversibility) | 1 | 34 |
| Health status | **Consider discontinuation**: | | |
| | • Limited life expectancy | 3 | 30-32 |
| | • Multimorbidity/increasing comorbidities | 3 | 30-32 |
| | • Frailty | 1 | 32 |
| | • Functional decline (physical or cognitive) | 1 | 32 |
| | • When harm (eg, polypharmacy, adverse drug reactions) may outweigh benefit | 2 | 30,32 |

phrased as suggestions (suggestions). To explore the context of recommendations for the discontinuation of statins applicable to older adults, we additionally analyzed the selected guidelines for other recommendations and considerations concerning statin treatment in older adults (defined as recommendations for adults aged ≥75 years or referred to as "old" or "older" adults/people/patients or "elderly," regarding all aspects of treatment). These recommendations were then synthesized into short statements and summarized into groups with related content. In a supplementary analysis, we checked whether the content of the recommendations concerning older adults in the excluded guidelines matched that mentioned in the included guidelines.

## Registration of Protocol

The review protocol was registered in PROSPERO (CRD42018116424).

**Table 3. Distribution of General Recommendations for Statin Treatment for Older Adults in the 18 Included Guidelines**

| | Recommendation | Limited to initiating therapy no. of guidelines | Guideline reference | Regarding therapy in general no. of Guidelines | Guideline reference |
|---|---|---|---|---|---|
| Drug safety related | Extravigilance, beware of adverse effects | 2 | 31,45 | 5 | 29,30,32,36,40 |
| | (Consider) a lower (start or target) dose | 3 | 29,35,40 | 4 | 31,32,34,45 |
| | Take into account drug-drug interactions | 1 | 45 | 3 | 29,32,34 |
| | Take into account polypharmacy | 2 | 41,42 | 6 | 29,30,32,34,36,45 |
| | Take into account pharmacokinetic/dynamic changes | 1 | 40 | 4 | 29,32,36,45 |
| | Take into account risks and benefits | 5 | 32,41-43,45 | 6 | 28,30,32,34,37,38 |
| Health related | Take into account: | | | | |
| | • life expectancy | 5 | 36,41,42,44,45 | 6 | 28,30,32,36,37,43 |
| | • comorbidities/multimorbidity | 5 | 31,40-43 | 6 | 29,32,36,45,47,48 |
| | • quality of life | 3 | 44,45 | | |
| | • frailty | 2 | 41,42 | 4 | 28,32,34,36 |
| | • health status | - | - | 1 | 28 |
| | • potential benefits from lifestyle modifications | 2 | 41,42 | | |
| | • costs | | | 1 | 34 |
| | • variability in physical functions | | | 1 | 36 |
| | • cognitive decline | | | 1 | 32 |
| | • vital prognosis | | | 1 | 36 |
| Preference and judgment | Take into account (informed) patient preference | 4 | 41-43,45 | 4 | 32,34,37,38 |
| | Shared decision making | 3 | 28,42,43 | 4 | 30,32,34,41 |
| | Take into account: priorities of care | 1 | 31 | - | - |
| Start or continue | • Continue treatment for those aged >75 y if well tolerated | | | 5 | 28,31,32,40,45 |
| | • Reconsider the recommendation to treat periodically | | | 2 | 32,40 |
| | • Screening for dyslipidemia for those aged >75 y or in patients with limited life expectancy: may not be appropriate/is recommended to be stopped | 2 | 28,31 | | |
| | • For secondary prevention, treatment with statins is recommended for older adults in the same way as for younger patients | 1 | 29 | | |

## RESULTS

A total of 9502 records were identified by database searching, 3368 of which were duplicate records. Of the 6134 remaining records, 6060 were found to be irrelevant (not guidelines or of different topics) based on title or abstract. We identified an additional 60 records from other websites from which we excluded 37 as duplicate records. These searches finally yielded 97 potentially relevant records to be screened for eligibility, of which 64 were excluded for reasons described in Figure 1 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart).[27] During the consensus meetings, the investigators agreed that summary documents, which provide guidelines without the full scientific background, were also to be excluded.

The remaining 33 records were guidelines containing recommendations for statin treatment in the general adult population that originated from 11 different countries/regions (Australia, Canada, Europe, Japan, Malaysia, Philippines, Singapore, Taiwan, United Kingdom, United States, and Qatar). Of these 33 guidelines, 15 (45%) did not include recommendations regarding statin discontinuation applicable to older adults at all, not even discontinuation for reasons such as contraindications, and were, therefore, excluded from the study.

The remaining 18 international guidelines were included in this study, and the primary characteristics of these guidelines are described in Table 1. With the exception of one guideline,[31] none of the guidelines included an upper age limit in the description of the population covered. Four guidelines stated that recommendations for certain populations, such as people with limited life expectancy, were not included.[30,31,42,44] Sixteen guidelines (excluding two[19,46]) included recommendations for both primary and secondary prevention. One guideline[46] did not include a quality grading system for assessment of the level of evidence supporting the recommendations. All guidelines included one or more expert or consensus-based recommendations.

### Information Synthesis

#### Recommendations for Statin Discontinuation Applicable to Older Adults

We identified two groups of recommendations regarding (at least temporary) statin discontinuation that were also applicable to older adults, specifically statin intolerance and health status. An overview of statin discontinuation recommendations can be found in Table 2. Recommendations regarding statin intolerance were present in all 18 guidelines included in this study and related to muscle symptoms (including rhabdomyolysis), elevation of transaminase levels, and the presence of contraindications. In 16 of the 18 guidelines, these recommendations were formulated in directive words ("should" or "have to be" discontinued) or named as a contraindication (instructions). None of the guidelines reported instructions for statin discontinuation that were exclusively aiming at older adults. Three guidelines[30-32] included suggestions for statin discontinuation in patients with (development of) poor health status, such as patients with functional decline during treatment or a limited life expectancy (see category "health status" in Table 2). These suggestions used phrases such as "it might be reasonable to consider statin discontinuation" in patients with short life expectancy, multimorbidity or increasing comorbidities, frailty, or functional decline, or when harm outweighs benefit. One guideline recommended that statins should only be considered in primary prevention

**Table 4. Scaled Domain Scores of AGREE II Instrument for the Included Guidelines**

| Guideline | Scope and purpose | Stakeholder involvement | Rigor of development | Clarity of presentation | Applicability | Editorial independence | Overall |
|---|---|---|---|---|---|---|---|
| Allan et al[28] | 89 | 78 | 59 | 83 | 56 | 50 | 50 |
| Catapano et al[29] | 83 | 50 | 60 | 94 | 83 | 54 | 83 |
| Downs et al[30] | 86 | 78 | 77 | 94 | 54 | 58 | 83 |
| Fan et al[31] | 78 | 25 | 27 | 83 | 27 | 29 | 42 |
| Grundy et al[32] | 89 | 78 | 78 | 94 | 58 | 71 | 83 |
| Guerrero[33] | 83 | 31 | 65 | 78 | 42 | 8 | 58 |
| Jacobson et al[34] | 83 | 72 | 55 | 86 | 54 | 50 | 67 |
| Jellinger et al[35] | 94 | 64 | 75 | 89 | 67 | 71 | 75 |
| Kinoshita[36] | 43 | 17 | 28 | 48 | 18 | 33 | 33 |
| Last et al[37] | 31 | 8 | 41 | 75 | 13 | 13 | 17 |
| Lewis[38] | 33 | 8 | 4 | 33 | 13 | 13 | 17 |
| Li et al[39] | 50 | 44 | 30 | 78 | 15 | 17 | 33 |
| MoH Malaysia[40] | 97 | 61 | 78 | 81 | 63 | 71 | 67 |
| MoH Qatar[41] | 44 | 39 | 21 | 72 | 23 | 63 | 25 |
| NICE[42] | 92 | 78 | 81 | 86 | 88 | 67 | 92 |
| NVDPA[43] | 89 | 94 | 81 | 94 | 92 | 96 | 92 |
| SIGN[44] | 94 | 94 | 94 | 100 | 94 | 92 | 100 |
| Tai et al[45] | 44 | 50 | 40 | 94 | 38 | 25 | 33 |

*Note*: Percentage of maximum scaled domain score, based on two appraisers. For details on the calculation, see Supplementary Text S2.
Abbreviations: MoH, Ministry of Health; NICE, National Institute for Health and Care Excellence; NVDPA, National Vascular Disease Prevention Alliance; SIGN, Scottish Intercollegiate Guidelines Network.

in cases with at least 3 or more years of life expectancy.[36] However, the guideline did not explicitly recommend statin discontinuation in those already on statin treatment. An overview of recommendations concerning statin discontinuation is provided in Supplementary Table S3.

### *Other Recommendations Regarding Statin Treatment in Older Adults*

The context of recommendations on statin discontinuation applicable to older adults was further explored by analyzing which other recommendations were formulated in relation to statin treatment in older adults. We found that 16 of the 18 guidelines included at least one recommendation concerning statin treatment in older adults. Across guidelines, the lower age limit defining older adults ranged from 65 years and older to 85 years and older or was not provided. We differentiated four groups of recommendations regarding statin treatment in older adults, including: (*a*) recommendations related to drug safety, including the need for extra vigilance for adverse effects, a lower (start) dose, or a higher low-density lipoprotein target (n = 15 guidelines); (*b*) health-related recommendations, including recommendations to take into account factors such as comorbidities or frailty (n = 15 guidelines); (*c*) recommendations related to taking patient preference into account and/or to base treatment decisions on clinical judgment (n = 11 guidelines); and (*d*) recommendations regarding starting and continuing statin treatment (n = 7 guidelines). Details on how these recommendations should be implemented in practice were not provided. In Table 3, the distribution of these recommendations (summarized into short statements) in the guidelines is described. The relevant full recommendations can be found in Supplementary Table S2.

### Quality Assessment

Table 4 summarizes the quality appraisals by scaled AGREE domain scores. The domains *clarity of presentation* and *scope and purpose* were assigned the highest median scores of 84.5% (range = 33%-100%) and 83% (range = 31%-97%), respectively. The domains *applicability* and *editorial independence* were assigned the lowest median scores of 54% (range = 13%-94%) and 52% (range = 8%-96%), respectively, making them the least well-addressed domains. The widest range of scores observed was in the domain *rigor of development* (range = 4%-94%; median = 62.5%). On overall assessment, 11 guidelines scored 50% or greater and were considered to be of moderate or good quality. The overall ICC was 0.90 (95% confidence interval = 0.89-0.92), indicating excellent interrater agreement.[47]

Visual inspection of the data did not show a relation between the overall quality of the guidelines and number of recommendations concerning older adults.

### Supplementary Analyses

The recommendations for statin treatment in older adults, provided by the 15 excluded guidelines, were of similar content compared to those discussed in this review, in paragraph "Other Recommendations Regarding Statin Treatment." Supplementary Table S3 shows an overview of the guidelines included in the supplementary analysis.

## DISCUSSION

In this systematic review of international guidelines for cardiovascular disease prevention in the general population, we searched for recommendations concerning statin discontinuation applicable to older adults. We found that 18 (55%) of the 33 eligible guidelines provided one or more recommendations for discontinuation of statin treatment. Remarkably, the other 15 guidelines (45%) did not include any recommendations regarding statin discontinuation applicable to older adults, not even discontinuation for reasons such as contraindications. All the 18 included guidelines provided recommendations related to statin intolerance; however, none of these was exclusively for older adults. Sixteen guidelines contained instructions and three guidelines provided recommendations formulated as suggestions to consider statin discontinuation in (older) patients with poor health status. In addition, 16 of the included guidelines also provided other recommendations for statin treatment in older adults. Safety considerations were the most common recommendations, mostly formulated in general terms.

In a systematic review of guidelines and recommendations concerning primary cardiovascular disease prevention for older adults (search dates between April and December 2013), Jansen and colleagues noted that none of the included guidelines considered discontinuation of medication in older adults.[48] We noticed that some progress has been made since 2013. We found three guidelines that reported at least some recommendations regarding poor health in the context of statin discontinuation.[30-32] The latter were not exclusive to but were at least more prominent in older adults. Furthermore, the most recently updated guideline included in our study, the 2018 American College of Cardiology/American Heart Association (ACC/AHA) guideline on management of blood cholesterol, is the first guideline to include an extensive discussion on statin discontinuation and age-related complexities in the preventive treatment of older adults.[32] It was unique in using the terms "deprescribing", "frailty," and "functional decline" in the context of statin discontinuation. However, in our view, the recommendations regarding statin discontinuation in this guideline were still formulated as suggestions ("it may be reasonable to"). Although factors are mentioned in the guideline that limit the potential benefits of statin treatment in older adults, such as frailty and functional decline, actually, these factors still do not have a clear circumscription. Therefore, it remains the physician's personal judgment to interpret to what extent the recommendations are applicable on an individual patient.

Our findings likely reflect the lack of high-quality evidence, including functional aspects and frailty, derived from well-designed statin treatment randomized controlled trials in older people, as well as the scarcity of trials focused on deprescribing.[46,49] One guideline reported a search for evidence supporting discontinuation of statin treatment in people aged 85 years and older and found only one eligible study.[17,44] However, the lack of high-level evidence cannot fully account for our findings, since previous research has shown that many recommendations in international cardiovascular disease prevention guidelines (up to 48%) are based on low-level evidence.[50] Furthermore, most of the guidelines in our study included recommendations based on

low-level evidence, including expert opinion. Other factors, such as a lack of awareness among guideline developers, potential conflicts of interest, and the absence of a deprescribing tradition, might explain the scarcity of deprescribing recommendations in current disease-centered guidelines.[50] In line with this argument, higher methodological quality scores measured with the AGREE II tool did generally not coincide with more recommendations for older adults.

### Strengths and Limitations

The strengths of this study include a comprehensive systematic search strategy and the use of a validated overall methodological quality appraisal (AGREE II tool) of the included clinical practice guidelines.[26] Also, this is the first study that provides an overview of recommendations for statin discontinuation. One of the limitations of this study was the exclusion of guidelines in languages other than English. We were aware of at least two non–English-language guidelines (in Norwegian and Dutch) that provide additional guidance on when to cease statin treatment in older adults, but they were not included in this review.[51,52] Nevertheless, our review did include insights from guidelines that originated from a broad range of geographical regions, including Australia, Asia, Europe, North America, and the Middle East. A second limitation may have been the summary of discontinuation recommendations into short statements through which some information was lost. To counteract this, we include an overview of all recommendations used in the information synthesis (Supplementary Tables S1 and S2).

### Conclusion and Future Directions

Although clinically relevant, the subject of statin discontinuation in older adults gets little attention in current international cardiovascular prevention guidelines, resulting in a lack of clear guidance for physicians reconsidering statin treatment in older adults with complex health problems. In this population, physicians will have to decide to continue or discontinue statins based on personal judgment, since evidence concerning the optimal duration of statin treatment in older frail adults or adults with multimorbidity is currently lacking.[46,49,50,53] Grants to develop randomized trials on deprescribing in older adults will probably result in more evidence for deprescribing. Until higher-level evidence becomes available, we suggest that new guidelines strive to combine available evidence with expert opinion and consensus techniques, to accommodate the need among physicians for more detailed recommendations regarding the implementation of deprescription of statins in practice. Issues, such as declining health status and short life expectancy, can already be discussed in guidelines as considerations for deprescription.

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**Conflicts of Interest:** None.

**Author Contributions:** M.A.P: literature search and selection, quality assessment of the guidelines, preparation of the manuscript, analysis and interpretation of data, and study design.

C.F.: quality assessment of the guidelines, preparation of the manuscript, and interpretation and analysis of data.

W.P.A.: interpretation of data and critical revision of the manuscript.

J.M.K.B.: study design and critical revision of the manuscript.

J.G.: preparation of the manuscript, interpretation of data, and study design.

S.P.M.: interpretation of data and critical revision of the manuscript.

S.S.: interpretation of data and critical revision of the manuscript.

R.K.E.P.: preparation of the manuscript, interpretation of data, and study design.

Y.M.D.: literature search and selection, quality assessment of the guidelines, preparation of the manuscript, analysis and interpretation of data, and study design.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Supplementary Text S1:** Complete search strategy.

**Supplementary Text S2:** Detailed explanation of the rating process.

**Supplementary Table S1:** An Overview of Recommendations Concerning Statin Discontinuation Applicable to Older Adults in 18 International Guidelines

**Supplementary Table S2:** Overview of Recommendations for Statin Treatment in Older Adults in the 18 Included Guidelines

**Supplementary Table S3:** Overview of Excluded Guidelines